ClinicalEvidence

Asthma in adults (acute): magnesium sulfate treatment

Search date November 2014

Ruth H. Green

ABSTRACT

INTRODUCTION: About 10% of adults have suffered an attack of asthma, and up to 5% of these have severe disease that responds poorly to treatment. Patients with severe disease have an increased risk of death, but patients with mild to moderate disease are also at risk of exacerbations. Most guidelines about the management of asthma follow stepwise protocols. This overview does not endorse or follow any particular protocol, but presents the evidence about a specific intervention, magnesium sulfate. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of magnesium sulfate for acute asthma? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 50 studies. After deduplication and removal of conference abstracts, 24 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 10 studies and the further review of 14 full publications. Of the 14 full articles evaluated, one systematic review was updated and one systematic review was added at this update. We performed a GRADE evaluation for five PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for two comparisons based on information about the effectiveness and safety of magnesium sulfate (iv) versus placebo and magnesium sulfate (nebulised) plus short-acting beta2 agonists (inhaled) versus short-acting beta2 agonists (inhaled) alone.

QUESTIONS

INTERVENTIONS

ACUTE ASTHMA TREATMENTS

Likely to be beneficial

Unknown effectiveness

Key points

- About 10% of adults have suffered an attack of asthma, and up to 5% of these have severe disease that responds poorly to treatment. These people have an increased risk of death.

  Most guidelines about the management of asthma follow stepwise protocols. This overview does not endorse or follow any particular protocol, but presents the evidence about a specific intervention, magnesium sulfate.

  Inhaled short-acting beta$_2$ agonists given in conjunction with systemic corticosteroids are considered the mainstay of treatment for acute asthma exacerbations.

- The previous version of this overview on treatments for acute asthma in adults included a range of comparisons, such as controlled oxygen supplementation, corticosteroids, corticosteroids (inhaled), education about acute asthma, formoterol (inhaled), helium-oxygen mixture (heliox), ipratropium bromide (inhaled) plus short-acting beta$_2$ agonists (inhaled), magnesium sulfate (nebulised), mechanical ventilation for people with severe acute asthma, oral corticosteroids alone, short-acting beta$_2$ agonists, short-acting beta$_2$ agonists delivered by metered-dose inhalers plus spacer devices/holding chambers, and specialist care.

- This updated overview focuses on magnesium sulfate (iv) alone and magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists. Magnesium sulfate is an airway smooth muscle relaxant that has been used as a bronchodilator in patients with acute asthma. Its safety and efficacy have not previously been confirmed, and its use has been considered controversial.

  As a result, the use of magnesium sulfate in acute asthma has been the focus of several studies published since the previous version of this overview. In contrast, there have been very few studies of other treatments of acute asthma in adults since the last overview.

  We have searched for evidence from RCTs and systematic reviews of RCTs on the effectiveness and safety of magnesium sulfate (iv) alone and magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists in adults with acute asthma.

- We don't know if adding nebulised magnesium to inhaled beta$_2$ agonists improves lung function in people with acute asthma.

  There is insufficient evidence to demonstrate a beneficial effect on lung function, symptoms, or hospital admissions when nebulised magnesium is added to standard therapy. Some studies suggest that patients presenting with severe disease may benefit, but the data are not conclusive.

- The use of iv magnesium sulfate in adults with acute asthma appears to have a modest effect in reducing hospital admissions in patients who have failed to respond to standard therapy and may prevent seven admissions for every 100 patients.

We don't know whether iv magnesium sulfate is more effective for patients who present with a more severe attack.

We don't know the optimum dose or method of administration of iv magnesium sulfate in acute asthma exacerbations.

We don't know whether iv magnesium sulfate improves clinical outcomes if given to patients with acute asthma in the pre-hospital setting.

Intravenous magnesium sulfate appears to be well tolerated without significant adverse effects, other than minor flushing.

Clinical context

GENERAL BACKGROUND

Asthma is a common and heterogeneous chronic condition affecting 1 in 12 adults in the UK, characterised by variability in clinical symptoms and airflow obstruction. Sudden severe exacerbations or acute attacks of asthma may be unpredictable and life threatening; many occur in patients with severe asthma, but patients with mild disease are also at risk. Acute asthma often develops slowly over several hours, meaning that there is often sufficient time for therapeutic intervention to prevent hospital admissions. Despite this, there were 54,300 emergency hospital admissions for acute asthma in the UK in the 12 months to May 2014.

FOCUS OF THE REVIEW

There has been a lack of recent studies of the treatment of adults with acute severe asthma, with the exception of those evaluating the effects of magnesium sulfate. Magnesium sulfate is an airway smooth muscle relaxant that has been used as a bronchodilator in patients with acute asthma in conjunction with standard therapy. Its safety and efficacy have not previously been confirmed, and its use has been considered controversial.

COMMENTS ON EVIDENCE

Interpretation of the studies of inhaled and intravenous magnesium sulfate in acute asthma in adults is hindered by wide variations in study methods. Particularly important are the differences in treatments given to control populations, which reflect variation in standard treatment guidelines between different healthcare settings. The use of systemic corticosteroids, nebulised beta$_2$ agonists, and additional nebulised ipratropium is widely considered by clinicians to provide optimum treatment; and we have evaluated the evidence for magnesium as an additional treatment rather than an alternative bronchodilator. Some studies have suggested that magnesium treatment, particularly via the intravenous route, has a particular benefit in patients who present with severe features but, again, interpretation of the data here is difficult due to inconsistencies in the definition and categorisation of severity. Given the heterogeneous nature of asthma, this is an important caveat. Furthermore, many studies exclude patients with life-threatening asthma, making it difficult to generalise the findings to this patient population. This is problematic because, outside of clinical trials, it is often those patients presenting with life-threatening features who are considered for magnesium therapy when standard treatment regimens fail to control the disease. Additional limitations in the available evidence relate to differences in the dose, route, and precise method of administration of magnesium; and it remains possible that alternative dose regimens may have different effects. An important aim of treatment is to prevent hospital admissions, but consideration of this outcome variable between different trials is also problematic because hospital admission rates are likely to be dependent on several factors, including the organisation of healthcare, delays in presentation, psychosocial factors, and the availability and quality of community care. The findings of this overview are confined to acute asthma in adults; there appears to be a differential benefit from intravenous magnesium in children, and paediatric studies are not considered in this evaluation.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, April 2010, to November 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 50 studies. After deduplication and removal of conference abstracts, 24 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 10 studies and the further review of 14 full publications. Of the 14 full articles evaluated, one systematic review was updated and one systematic review was added at this update.

DEFINITION Asthma is a common and heterogeneous chronic condition affecting 1 in 12 adults in the UK, [1] characterised by variability in clinical symptoms and airflow obstruction. Sudden severe exacerbations or acute attacks of asthma may be unpredictable and life threatening; many occur in patients with severe asthma, but patients with mild disease are also at risk. Acute asthma often develops slowly over several hours, meaning that there is often sufficient time for therapeutic intervention to prevent hospital admissions. Despite this, there were 54,300 emergency hospital admissions for acute asthma in the UK in the 12 months to May 2014. [2] Acute asthma is defined here as an

exacerbation of underlying asthma requiring urgent treatment. Most guidelines about the management of asthma follow stepwise protocols. This overview does not endorse or follow any particular protocol, but it focuses on the effectiveness and safety of magnesium sulfate (iv) alone and magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists in adults with acute asthma.

INCIDENCE/ PREVALENCE

The lack of a gold-standard definition of asthma, along with increasing recognition of the condition as a heterogeneous disease, [3] make the interpretation of epidemiological studies particularly challenging in asthma. The reported prevalence of asthma has been increasing worldwide, but may have currently reached a plateau. [4] [5] [6] About 10% of people have suffered an attack of asthma, but epidemiological studies have also found marked variations in prevalence between and within countries. [4] [7]

AETIOLOGY/ RISK FACTORS

Asthma is increasingly recognised as a heterogeneous condition with a range of clinically distinct phenotypes that are likely to have distinct aetiologies. [3] The risk of asthma is thought to be greatest in individuals with a genetic predisposition who are exposed to environmental stimuli that may have an allergic or irritant effect. [8] Approximately 50% of asthma occurs before the age of 10 years, and early life events (including low birth weight, early childhood infections, and environmental exposure to pollutants, tobacco smoke, and allergens) have all been causally implicated. Adult-onset asthma has been associated with rhinitis, smoking, weight gain, occupational exposures, and some drugs, including aspirin. [9] The risk factors for acute severe exacerbations of asthma are similarly diverse and may include respiratory viral or bacterial infections, exposure to dietary or inhaled allergens or irritants in the inhaled environment, and psychosocial factors such as emotional upset. [10]

PROGNOSIS

About 10% to 20% of people presenting to the emergency department with asthma are admitted to hospital. Of these, less than 10% receive mechanical ventilation. [11] [12] Those who are ventilated are at 19-fold increased risk of ventilation for a subsequent episode. [13] It is unusual for people to die unless they have suffered respiratory arrest before they reach hospital. [14] One prospective study of 939 people discharged from emergency care found that 106/641 (17%, 95% CI 14% to 20%) relapsed by 2 weeks. [15] It is thought that as many as 75% of asthma admissions are preventable, [1] and a recent UK-wide national review of asthma deaths concluded that the majority of deaths were avoidable, with preventable factors identified in two-thirds of cases. [16]

AIMS OF INTERVENTION

To minimise or eliminate symptoms; to maximise lung function; to prevent hospital admissions; to prevent exacerbations; to minimise the need for medication; to improve quality of life; to minimise adverse effects of treatment; and to provide enough information and support to facilitate self-management of asthma.

OUTCOMES

Symptom severity (daytime and nocturnal, excluding lung function); **lung function**, in terms of peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1), need for rescue medication (such as inhaled beta$_2$ agonists), variability of flow rates, and activities of daily living; **hospital admissions** (includes re-admission and discharge); **quality of life**; and **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date November 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to November 2014, Embase 1980 to November 2014, The Cochrane Database of Systematic Reviews 2014, issue 11 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews of RCTs and RCTs published in English, containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. No restriction was placed on level of blinding of studies. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse

effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported interventions from this overview: Controlled oxygen supplementation; Corticosteroids; Corticosteroids (inhaled); Education about acute asthma; Formoterol (inhaled); Helium–oxygen mixture (heliox); Ipratropium bromide (inhaled) plus short-acting $beta_2$ agonists (inhaled); Mechanical ventilation for people with severe acute asthma; Oral corticosteroids alone; Short-acting $beta_2$ agonists; Short-acting $beta_2$ agonists delivered by metered-dose inhalers plus spacer devices/holding chambers; Specialist care. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of magnesium sulfate for acute asthma?

OPTION MAGNESIUM SULFATE (IV) VERSUS PLACEBO

- For GRADE evaluation of interventions for Asthma in adults (acute): magnesium sulfate treatment, see table, p 13 .
- The use of iv magnesium sulfate in adults with acute asthma appears to have a modest effect in reducing hospital admissions in patients who have failed to respond to standard therapy.
- It has previously been thought that the benefit of iv magnesium may be confined to patients presenting with more severe disease, but the current evidence does not confirm this and more studies are needed. The effects of iv magnesium in patients presenting with life-threatening asthma are not known.
- Studies have demonstrated large variations in prescribing procedures for acute asthma. The optimum dose, method, frequency, and timing of administration of iv magnesium sulfate, and the most effective combinations of co-medication are not known.
- We don't know whether iv magnesium sulfate improves clinical outcomes if given to patients with acute asthma in the pre-hospital setting.
- Intravenous magnesium appears to be well tolerated without significant adverse effects other than minor flushing.

Benefits and harms

IV magnesium sulfate versus placebo:

We found one systematic review (search date 2014, 14 RCTs, 2313 adults with acute asthma). [17]

Symptom severity

IV magnesium sulfate compared with placebo IV magnesium sulfate seems no more effective than placebo at improving symptoms of breathlessness in people with acute asthma (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Borg dyspnoea scale					
[17] Systematic review	Adults with acute asthma 4 RCTs in this analysis	**Borg dyspnoea scale** with iv magnesium sulfate with placebo 485 people in this analysis One of the RCTs in this analysis involved treatment with ipratropium, which has been found to affect hospital admission rates without affecting the degree of airflow obstruction [18]	MD –0.22 95% CI –0.55 to +0.12	⟷	Not significant

Lung function

IV magnesium sulfate compared with placebo IV magnesium sulfate may be more effective than placebo at improving lung function in people with acute asthma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[17] Systematic review	Adults with acute asthma 4 RCTs in this analysis	**FEV_1 (% predicted)** with iv magnesium sulfate with placebo 523 people in this analysis One of the RCTs in this analysis involved treatment with ipratropium, which has been found to affect hospital admission rates without affecting the degree of airflow obstruction [18]	MD 4.41 95% CI 1.75 to 7.06 P = 0.0011	○○○	iv magnesium sulfate
[17] Systematic review	Adults with acute asthma 8 RCTs in this analysis	**PEF (L/minute)** with iv magnesium sulfate with placebo 1460 people in this analysis 3 of the RCTs in this analysis involved treatment with aminophylline, and 2 RCTs with ipratropium, both of which have been found to affect hospital admission rates without affecting the degree of airflow obstruction [18]	MD 17.40 95% CI 8.64 to 26.17 P <0.0001 Statistically significant heterogeneity was identified in the analysis (I^2 = 50%; P = 0.05) See Further information on studies	○○○	iv magnesium sulfate

Hospital admissions

IV magnesium sulfate compared with placebo IV magnesium sulfate may be more effective than placebo at reducing hospital admissions in people with acute asthma, particularly when used in conjunction with nebulised ipratropium bromide (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admissions					
[17] Systematic review	Adults with acute asthma 11 RCTs in this analysis	**Hospital admissions** 469/891 (53%) with iv magnesium sulfate 503/878 (57%) with placebo One of the RCTs in this analysis involved treatment with amino-	OR 0.75 95% CI 0.60 to 0.92 P = 0.0066	●○○	iv magnesium sulfate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		phylline and 4 RCTs involved ipratropium, both of which have been found to affect hospital admission rates without affecting the degree of airflow obstruction [18]			
[17] Systematic review	Adults with severe airflow obstruction 6 RCTs in this analysis Subgroup analysis See Further information on studies	**Hospital admissions** 100/219 (46%) with iv magnesium sulfate 118/255 (46%) with placebo One of the RCTs in this review involved treatment with aminophylline and 2 RCTs involved ipratropium, both of which have been found to affect hospital admission rates without affecting the degree of airflow obstruction [18]	OR 0.87 95% CI 0.58 to 1.31 Statistically significant heterogeneity was identified in the analysis (I^2 = 57%; P = 0.04)	⟷	Not significant
[17] Systematic review	Adults with acute asthma 4 RCTs in this analysis Subgroup analysis Pre-specified subgroup analysis of RCTs in which people also received nebulised ipratropium bromide	**Hospital admissions** 375/550 (68%) with iv magnesium sulfate plus nebulised ipratropium bromide 386/522 (74%) with placebo plus nebulised ipratropium bromide	OR 0.73 95% CI 0.55 to 0.96	●○○	iv magnesium sulfate
[17] Systematic review	Adults with acute asthma 7 RCTs in this analysis Subgroup analysis Pre-specified subgroup analysis of RCTs in which people did not receive nebulised ipratropium bromide	**Hospital admissions** 94/341 (28%) with iv magnesium sulfate 117/356 (33%) with placebo	OR 0.77 95% CI 0.55 to 1.06	⟷	Not significant
[17] Systematic review	Adults with acute asthma 2 RCTs in this analysis	**Hospital re-admission rates** 8/461 (2%) with iv magnesium sulfate 3/426 (1%) with placebo One of the RCTs in this analysis involved treatment with ipratropium, which has been found to affect hospital admission rates without affecting the degree of airflow obstruction [18]	OR 2.30 95% CI 0.66 to 7.99 P = 0.19	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] Systematic review	People with asthma 8 RCTs in this analysis	**Adverse effects** with iv magnesium sulfate with placebo Absolute results not reported The review noted considerable variation across RCTs in reporting of adverse effects, which prevented synthesis of data on this outcome The review authors noted that the most commonly reported adverse effects were flushing, fatigue, nausea, and headache			

Further information on studies

[17] *Treatment* People receiving iv magnesium sulfate are likely to have severe disease and are, therefore, likely to receive treatment before iv magnesium sulfate. In all the RCTs included in the review, people were also treated with nebulised beta$_2$ agonists. In most RCTs, oxygen and corticosteroids were also given concomitant to allocated treatment. Other co-interventions used across trials were theophylline, aminophylline, and ipratropium. The routes, frequency and dose of administration of additional treatments varied across studies.

[17] *Lung function: heterogeneity in analysis* The authors carried out a sensitivity analysis for PEF using change from baseline instead of endpoint means, with a resulting substantial reduction in the magnitude of effect (MD 9.44, 95% CI 2.07 to 16.81).

[17] *Hospital admissions: subgroup analysis by severity of disease* Pre-specified subgroup analysis of adults with PEF between 33% and 50% at presentation. When baseline PEF was not available, or when the value was close to a cutoff, other criteria were consulted, and the value was then standardised across trials using studies reporting several indices.

Comment: Further studies are needed to clarify the role of iv magnesium sulfate in acute asthma, and to compare it with standard treatment, including bronchodilators and systemic corticosteroids.

Clinical guide

We found evidence to support the use of intravenous magnesium, given as an infusion to patients presenting to the emergency department with acute severe asthma who have failed to respond to standard therapy, including nebulised short-acting beta$_2$ agonists, ipratropium bromide, and systemic corticosteroids. It should be emphasised that this is an add-on therapy and should not be considered as a substitute for beta$_2$ agonists or corticosteroids. There is insufficient evidence to evaluate the role of iv magnesium in patients with life-threatening asthma as they were excluded from the clinical trials. Nonetheless, since iv magnesium appears safe and well tolerated, many clinicians advocate a therapeutic trial of iv magnesium in this group, with the caveat that its administration should not delay appropriate alternative treatment such as intubation and ventilation in those with a near-fatal presentation.

Magnesium sulfate is contraindicated in patients with hypermagnesaemia, hyperkalemia (renal insufficiency), and myasthenia gravis. Hypermagnesaemia may lead to with muscle weakness and may be reversed by the administration of its physiological antagonist, calcium gluconate.

The results of the systematic review, [17] on which this update is based, are heavily weighted by a single RCT, (the 3MG trial) which randomised 784 adults presenting with asthma exacerbations to receive nebulised magnesium, iv magnesium, or placebo alongside standard therapy. [19] The

authors found a trend towards a reduction in hospital admissions, but this was not statistically significant, and they concluded that it was not possible to demonstrate a clinically useful benefit with this treatment. When these results were combined with previous studies in the meta-analysis, however, a significant reduction in the chance of being admitted to hospital with acute asthma was demonstrated for iv magnesium compared to placebo. The majority of the other trials included in the meta-analysis were confined to small numbers of people and were insufficiently powered to demonstrate an effect on hospital admissions. There were important differences in study design, but the findings remained when unpublished and non-randomised studies were excluded. The data, therefore, suggest that there is 95% confidence that between 2 and 13 fewer adults with acute asthma will be admitted to hospital for every 100 patients treated with iv magnesium. The interpretation of clinical studies in this emergency care setting is limited by differences in standard treatment of acute severe asthma, with some centres using nebulised ipratropium and/or iv aminophylline on top of nebulised beta$_2$ agonists and corticosteroids. Furthermore, the risk of hospital admission is likely to vary in different health care settings depending on the quality of care and availability of support in the community.

These results of an earlier systematic review [20] suggested that the benefits of iv magnesium on the risk of hospital admission and lung function were confined to patients presenting with more severe acute asthma. A later meta-analysis, [21] published before the 3Mg trial, concluded that iv magnesium led to a modest improvement in lung function but no significant reduction in hospital admissions. The findings of the most recent review, [17] reported above, did not confirm that the benefit of iv magnesium was confined to severe patients; however, differences in the definition and recording of severity between studies made this difficult to interpret. Three studies that used markers of severity at presentation to subgroup participants did demonstrate a greater benefit in terms of hospital admission in the more severe groups. [22] [23] [24] One further limitation is that the 3Mg study excluded patients with life-threatening asthma; [19] if the finding that more severe patients have greater benefit is real, then excluding this group may have led to under-estimation of the benefits.

OPTION MAGNESIUM SULFATE (NEBULISED) PLUS SHORT-ACTING BETA2 AGONISTS (INHALED) VERSUS SHORT-ACTING BETA2 AGONISTS (INHALED) ALONE

- For GRADE evaluation of interventions for Asthma in adults (acute): magnesium sulfate treatment, see table, p 13 .
- We don't know if adding nebulised magnesium to inhaled beta$_2$ agonists (with or without ipratropium bromide) improves lung function in people with acute asthma.
- We found insufficient evidence to evaluate the role of nebulised magnesium in addition to inhaled beta$_2$ agonists on symptoms and quality of life in acute asthma.
- There is no clear evidence that nebulised magnesium sulfate given in addition to standard treatment reduces hospital admissions.
- Nebulised magnesium plus inhaled short-acting beta$_2$ agonists may result in an improvement in lung function in patients presenting with severe exacerbations compared to inhaled short acting beta$_2$ agonists alone. However, the evidence is limited and further studies are still needed to address whether patients with severe features would benefit.
- Nebulised magnesium appears to be well tolerated in acute asthma.

Benefits and harms

Magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists (inhaled) versus short-acting beta$_2$ agonists (inhaled) alone:

We found one systematic review (search date 2012, 7 RCTs, 389 adults and children). [25] We found one subsequent RCT comparing nebulised magnesium plus standard care with placebo plus standard care. [19] However, inhaled short acting beta$_2$ agonist were not consistently given to either group, therefore, we have reported this study in the Comment section, p 8 .

Symptom severity

No data from the following reference on this outcome. [25]

Lung function

Nebulised magnesium sulfate plus inhaled short-acting beta$_2$ agonists compared with inhaled short-acting beta$_2$ agonists alone We don't know whether nebulised magnesium sulfate plus inhaled beta$_2$ agonists is more effective than inhaled beta$_2$ agonists alone at improving lung function (PEFR and FEV_1) in people with acute asthma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[25] Systematic review	Adults with acute asthma 2 RCTs in this analysis	**Forced expiratory volume in 1 second (FEV_1) , 60 minutes** with adding nebulised magnesium sulfate to beta$_2$ agonists with beta$_2$ agonists alone Absolute results not reported 136 people in this analysis People could also receive corticosteroids; see Further information on studies	SMD +0.18 95% CI –0.65 to +1.02 P = 0.67 Statistically significant heterogeneity present in analysis (I^2 = 81%, P = 0.002)	⟷	Not significant
[25] Systematic review	People with acute asthma 2 RCTs in this analysis One RCT in the analysis included children See Further information on studies	**Peak expiratory flow , up to 60 minutes** with adding nebulised magnesium sulfate to beta$_2$ agonists with beta$_2$ agonists alone Absolute results not reported 135 people in this analysis People could also receive corticosteroids; see Further information on studies	SMD +7.07 95% CI –11.69 to +25.84 P = 0.46	⟷	Not significant
[25] Systematic review	Adults with acute asthma 2 RCTs in this analysis	**Peak expiratory flow , discharge** with adding nebulised magnesium sulfate to beta$_2$ agonists with beta$_2$ agonists alone Absolute results not reported 26 people in this analysis People could also receive corticosteroids; see Further information on studies	SMD +0.68 95% CI –8.56 to +9.92 P = 0.89	⟷	Not significant
[25] Systematic review	Adults with severe asthma (FEV_1 or PEFR <50% predicted) Data from 1 RCT Subgroup analysis	**Forced expiratory volume at 1 second** with adding nebulised magnesium sulfate to beta$_2$ agonists with beta$_2$ agonists alone Absolute results not reported 52 people in this analysis	SMD 0.63 95% CI 0.07 to 1.19 P = 0.028	○○○	adding nebulised magnesium sulfate to beta$_2$ agonists

Hospital admissions

Nebulised magnesium sulfate plus inhaled short-acting beta$_2$ agonists compared with inhaled short-acting beta$_2$ agonists alone We don't know whether nebulised magnesium sulfate plus inhaled beta$_2$ agonists is more effective than inhaled beta$_2$ agonists alone at reducing the number of people with severe asthma admitted to hospital (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admissions					
[25] Systematic review	Adults with severe asthma (FEV_1 or PEFR <50% predicted) 2 RCTs in this analysis Subgroup analysis	**Proportion of people with severe asthma admitted to hospital , timeframe unclear** 13/47 (28%) with adding nebulised magnesium sulfate to $beta_2$ agonists 18/40 (45%) with $beta_2$ agonists alone	RR 0.62 95% CI 0.38 to 1.02 P = 0.06	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	Adults and children with acute asthma 3 RCTs in this analysis One RCT comprised entirely of children	**Proportion of people with mild to moderate adverse event , timeframe unclear** 24/106 (23%) with adding nebulised magnesium sulfate to $beta_2$ agonists 27/103 (26%) with $beta_2$ agonists alone People could also receive corticosteroids; see Further information on studies	RD –0.03 95% CI –0.14 to +0.08 P = 0.62	⟷	Not significant
[25] Systematic review	Adults and children with acute asthma 4 RCTs in this analysis	**Proportion of people with serious adverse event , timeframe unclear** 0/115 with adding nebulised magnesium sulfate to $beta_2$ agonists 0/108 with $beta_2$ agonists alone People could also receive corticosteroids; see Further information on studies	RD 0.00 95% CI –0.03 to +0.03 P = 1.0	⟷	Not significant

Further information on studies

[25] *Treatment* Corticosteroids were routinely administered as a co-intervention in the RCTs included in the review, but dose, timing, route, and frequency of administration varied widely across the studies. In one RCT, clinicians were free to administer whatever treatment they deemed necessary, and another RCT gave no other medication as a co-intervention.

[25] *Heterogeneity* The significant heterogeneity in forced expiratory volume in 1 second (FEV_1) was not further explained in the review. However, one study in adults with severe acute asthma (n = 52) routinely gave nebulised salbutamol and iv hydrocortisone at presentation, while in the other RCT (adults with moderate to severe acute

asthma, n = 74) systemic corticosteroids were administered if there was no improvement after the three doses of study treatment. The studies had a similar weight in the analysis.

Comment:

The systematic review found no significant difference in hospital admissions and pulmonary function between nebulised magnesium sulfate plus beta$_2$ agonists and beta$_2$ agonists alone; [25] however, a subgroup analysis indicates that adding nebulised magnesium sulfate to beta$_2$ agonists in people with acute severe asthma could be beneficial. [25] The systematic review noted that the control groups in the included studies were "surprisingly heterogeneous" and that RCTs are needed in which systemic corticosteroids, beta$_2$ agonists, and anticholinergics are administered to both groups.

The results from the 3Mg trial [19] were published after the meta-analysis [25] and, therefore, these data were not included in the pooled analysis. This RCT did not meet the *BMJ Clinical Evidence* inclusion criteria for this option; however, we report the results here for interest.The RCT (690 people with acute asthma) compared 500 micrograms nebulised magnesium (n = 332) with placebo (n = 358). The results were consistent with those from the meta-analysis, with no significant benefit from nebulised magnesium compared with placebo. Patients in this study were given optimal treatment with systemic corticosteroids, nebulised beta$_2$ agonists, and nebulised ipratropium. That magnesium conferred no additional benefit suggests that optimal bronchodilation may be achieved with this standard treatment regimen.

Clinical guide

Standard treatment for patients presenting with acute severe asthma depends on a careful assessment of severity and includes, for all patients, inhaled short-acting beta$_2$ agonists and systemic corticosteroids. The addition of ipratropium bromide and/or oxygen is appropriate for some patients. There is insufficient evidence to recommend the use of nebulised magnesium sulfate in addition to inhaled short-acting beta$_2$ agonists in the management of acute asthma in adults. There is weak evidence to suggest that nebulised magnesium sulfate given to patients presenting with severe disease may reduce hospital admission and improve lung function.

The largest RCT [26] included in the meta-analysis [25] randomised 100 patients presenting with acute severe or life-threatening asthma (defined on clinical characteristics and PEF) to receive placebo or 500 mg nebulised magnesium sulfate in addition to standard therapy, and found no difference between the two groups in PEF or hospital admissions. A smaller study [27] demonstrated improvements in post-bronchodilator FEV_1 and risk of hospital admission, in patients with acute asthma and FEV_1 at presentation less than 60%, with nebulised magnesium sulfate compared to placebo. Pooling all of the available data demonstrates no significant benefit from nebulised magnesium sulfate overall in acute asthma; however, comparison of individual trials is limited by numerous important differences in study design, including disease severity at randomisation and administered dose of magnesium. A beneficial effect in particular subgroups (such as those with more severe airflow obstruction) can, therefore, not be excluded.

The positive findings in two of the RCTs [27] [28] may reflect suboptimal treatment in the control population and do not provide sufficient evidence to recommend the use of nebulised magnesium in addition to standard therapy.

GLOSSARY

Borg Dyspnoea Scale A 10-point scale used to quantify the level of dyspnoea, where 0 is no difficulty in breathing and 10 is maximal dyspnoea.

Forced expiratory volume in 1 second (FEV_1) The volume breathed out in the first second of forceful blowing into a spirometer, measured in litres.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Peak expiratory flow rate (PEFR) The maximum rate that gas is expired from the lungs when blowing into a peak flow meter or a spirometer. It is measured at an instant, but the units are expressed as litres per minute.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists (inhaled) versus short-acting beta$_2$ agonists (inhaled) alone One systematic review updated. [25] Categorisation unchanged (unknown effectiveness).

Magnesium sulfate (iv) versus placebo One systematic review added. [17] Categorisation changed from 'unknown effectiveness' to 'likely to be beneficial'.

REFERENCES

1. Asthma UK. Asthma facts and FAQs. 2015. Available at http://www.asthma.org.uk/asthma-facts-and-statistics (last accessed 13 November 2015).
2. Health and Social Care Information Centre (HSCIC). Asthma emergency admissions: fall in August, rise in September. August 2014. Available at http://www.hscic.gov.uk/article/4989/Asthma-emergency-admissions-fall-in-August-rise-in-September (last accessed 13 November 2015).
3. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224.[PubMed]
4. Asher MI, Montefort S, Björkstén B, et al; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence ofsymptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743. [Erratum in: Lancet. 2007;370:1128.][PubMed]
5. Pearce N, Aït-Khaled N, Beasley R, et al; ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007;62:758–766.[PubMed]
6. Anandan C, Nurmatov U, van Schayck OC, et al. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010;65:152–167.[PubMed]
7. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355:2226–2235.[PubMed]
8. Henderson AJ. Aetiology of Asthma. *Paediatr Child Health* 2013;23:287–290.
9. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Rev* 2013;22:44–52.[PubMed]
10. Singh AM, Busse WW. Asthma exacerbations. 2: Aetiology. *Thorax* 2006;61:809–816.[PubMed]
11. FitzGerald JM, Grunfeld A. Acute life-threatening asthma. In: FitzGerald JM, Ernst PP, Boulet LP, et al, eds. Evidence based asthma management. Hamilton, ON: BC Decker, 2000:233–244.
12. Nahum A, Tuxen DT. Management of asthma in the intensive care unit. In: FitzGerald JM, Ernst PP, Boulet LP, et al, eds. Evidence based asthma management. Hamilton, ON: BC Decker, 2000:245–261.
13. Turner MT, Noertjojo K, Vedal S, et al. Risk factors for near-fatal asthma: a case control study in hospitalized patients asthma. *Am J Respir Crit Care Med* 1998;157:1804–1809.[PubMed]
14. Molfino NA, Nannimi A, Martelli AN, et al. Respiratory arrest in near-fatal asthma. *N Engl J Med* 1991;324:285–288.[PubMed]
15. Emmerman CL, Woodruff PG, Cydulka RK, et al. Prospective multi-center study of relapse following treatment for acute asthma among adults presenting to the emergency department. *Chest* 1999;115:919–927. [PubMed]
16. National Review of Asthma Deaths (NRAD), Royal College of Physicians. Why asthma still kills. August 2015. Available at https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills (last accessed 13 November 2015).
17. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. In: The Cochrane Library, Issue 11, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2014.
18. FitzGerald JM. Commentary: intravenous magnesium in acute asthma. *Evid Based Med* 1999;4:138.
19. Goodacre S, Cohen J, Bradburn M, et al; 3Mg Research Team. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial. *Lancet Respir Med* 2013;1:293–300.[PubMed]
20. Rowe BH, Bretzlaff JA, Bourdon C, et al. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med* 2000;36:181–190.[PubMed]
21. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. *Emerg Med J* 2007;24:823–830.[PubMed]
22. Bilaceroglu S, Akpinar M, Tiras A. Intravenous magnesium sulphate in acute asthma. Annual Thoracic Society 97th International Conference, San Francisco; 2001.
23. Bloch H, Silverman R, Mancherje N, et al. Intravenous magnesium sulfate as an adjunct in the treatment of acute asthma. *Chest* 1995;107:1576–1581.[PubMed]
24. Bradshaw TA, Matusiewicz SP, Crompton GK, et al. Intravenous magnesium sulphate provides no additive benefit to standard management in acute asthma. *Respir Med* 2008;102:143–149.[PubMed]
25. Powell C, Dwan K, Milan SJ, et al. Inhaled magnesium sulfate in the treatment of acute asthma. In: The Cochrane Library, Issue 11, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2012.
26. Aggarwal P, Sharad S, Handa R, et al. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. *Emerg Med J* 2006;23:358–362.[PubMed]
27. Gallegos-Solórzano MC, Pérez-Padilla R, Hernández-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjuvant management of severe asthma crisis in an emergency department. *Pulm Pharmacol Ther* 2010;23:432–437.[PubMed]
28. Hughes R, Goldkorn A, Masoli M, et al. Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomised placebo-controlled trial. *Lancet* 2003;361:2114–2117.[PubMed]

Ruth H. Green
Consultant Respiratory Physician and Honorary Senior Lecturer
Department of Respiratory Medicine
Glenfield Hospital
Leicester
UK

Competing interests: RHG has received funding from Novartis, Astra Zeneca, and Chiesi for attending and speaking at conferences.
We would like to acknowledge the previous contributors of this overview, including Chris Cates, Paul O'Byrne, Bazian Ltd, and Gustavo Rodrigo.

Disclaimer

GRADE **Evaluation of interventions for Asthma in adults (acute): magnesium sulfate treatment.**

Important outcomes			Hospital admissions, Lung function, Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of magnesium sulfate for acute asthma?									
4 (485) [17]	Symptom severity	IV magnesium sulfate versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for use of active co-interventions
12 (1983) [17]	Lung function	IV magnesium sulfate versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity in larger analysis; directness point deducted for use of active co-interventions
11 (1769) [17]	Hospital admissions	IV magnesium sulfate versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity in one subgroup analysis, and for difference in statistical significance of effect across subgroup analysis; directness point deducted for use of active co-interventions
At least 2 (at least 135) [25]	Lung function	Magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists (inhaled) versus short-acting beta$_2$ agonists (inhaled) alone	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among RCTs; directness point deducted for inclusion of active co-interventions and inclusion of children in one RCT
2 (87) [25]	Hospital admissions	Magnesium sulfate (nebulised) plus short-acting beta$_2$ agonists (inhaled) versus short-acting beta$_2$ agonists (inhaled) alone	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for inclusion of active co-interventions and for limitation to people with severe asthma

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.